Remarks

Applicants respectfully request that the above amendments be entered after final as they place the claims in better form for allowance.

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 9-23 are pending in the application, with 9-11, 21-23 being the independent claims. Claims 10 and 21-23 are sought to be amended. Support for amendments to the claims can be found, for example, *inter alia* at page 8, lines 15-21, page 15, lines 16-19, page 14, lines 1-11, page 14, lines 19-30, page 15, lines 1-2 and Figure 7 in the specification. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to the Claims

The Examiner has objected to claims 10, 13, 16, 19 and 22 for failing to further limit the subject matter of a previous claim. Applicants have amended claims 10 and 22 to place them in independent form. Claims 13, 16 and 19 depend directly or indirectly from 10.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 9-23 under 35 U.S.C. § 103(a) for allegedly being unpatenable over Catanzariti *et al. Biotechniques* 15:474-479 (1993)

("Catanzariti"), and in view of the combination of U.S. Patent 5,494,806 to Segre *et al.* ("Segre") and the Bringhurst *et al. Endocrinology* 132:2090-2098 (1993) publication ("Bringhurst"). Applicants respectfully traverse this rejection.

The Examiner maintains the rejection in part because "[t]he Bringhurst et al. and Segre et al. references provided ample motivation to express the **human PTHR** of Segre et al. in **LLC-PK1 cells** a [*sic*] described by Bringhurst et al. for the purpose of identifying agonists and antagonists thereto..." (Paper No. 19, page 3). Applicants disagree. The Bringhurst article describes an "*in vitro* model system in which PTH/PTHRP receptor function might be studied under more controlled circumstances..." (Bringhurst, p. 2090). Futhermore, Bringhurst describes using the model system for "study of issues such as the influence of receptor number on hormone binding and biological response(s) and the cross-talk between different intracellular signaling pathways activated homologously by PTH/PTHRP ligands or heterologously via calcitonin or other endogenous receptors" (Bringhurst, p. 2095). There is no motivation to use the system as described in Bringhurst to screen for agonists and antagonists of a receptor which couples to both Gs and Gq proteins. The Examiner is relying upon hindsight to suggest that Bringhurst suggests the use of the model system described for the claimed method.

Bringhurst could not have suggested the use of the model system for the claimed methods because at the time of publication, they did "not yet know precisely which G-proteins are coupled to the PTH/PTHR receptors expressed in LLC-PK_1 cells nor which one of them, other than Gs, might mediate the observed responses" (Bringhurst, p. 2096).

Furthermore, Bringhurst only describes expression of rat and oppossum PTHR in LLC-PK1 cells and provides no teaching on human PTHR.

Segre does not remedy the difficiencies of Bringhurst. Although Segre mentions LLC-PK1 cells in a list of preferred cells (column 19, lines 57-62), there is no indication that PTHR is functionally expressed in these cells. The only functional assays described in Segre were carried out in COS cells (See column 9). The Examiner also states that "...Catanzariti et al. provide the motivation to measure the activation of that human receptor in that cell line by measuring ligand-induced, **cyclic AMP-mediated urokinase activity**" (Paper No. 19, page 3). Catanzariti does describe the expression of a mouse $\beta_2$adrenergic receptor in LLC-PK1 cells and the subsequent measurement of Gs pathway activation through the measurement of urokinase plasminogen activator. However, there is nothing to suggest that receptors exist which also couple to the Gq pathway and that u-PA could be used to assay for agonists and antagonists of receptors which couple to both pathways.

The Examiner states that the "combination of references taught all of the limitations of the instant claims either explicity or inherently, and provided ample explicit motivation to combine those elements in the manner claimed." Paper No. 19, page 4). Applicants disagree. Specifically, the references fail to teach that 1) the human PTHR receptor or any other receptor can be linked to the Gs and Gq pathways; 2) the human PTHR receptor can be functionally expressed in LLC-PK1 cells; and 3) u-PA can be independently activated by the Gs and Gq pathways. Moreover, there is no motivation to combine the references to arrive at the claimed method without knowledge contained in the specification.

The Examiner states that the decision in *In re Dillion*

> "...further held that the 'discovery that claimed composition possesses property not disclosed for prior art does not alone defeat prima facie case.' This legal analysis is equally applicable to the method of the instant claims because the prior art provided specific motivation to practice a method that is fully encompassed by these claims and meets all of their limitations either explicitly or inherently" (Paper No. 15, p. 4) (emphasis added).

Applicants disagree. Although the Examiner may have provided the legal basis for the use of an inherency argument in an obviousness rejection, the Examiner provides no legal basis as to why the analysis of *In re Dillion* is equally applicable in this case. The claimed invention is not an old composition based on newly discovered properties. Rather, the invention is a method for screening compounds of a receptor which couples to both Gs and Gq pathways. Furthermore, as described above, the claimed method is not fully encompassed by the cited references explicitly or inherently.

Solely in an effort to expedite prosecution, Applicants have amended claims 21-23 to include an additional cell line in the method of the claimed invention. The additional cell line has inhibited Gs pathway signaling. Thus, a compound which was an agonist of a receptor which couples to both Gs and Gq would still be able to induce u-PA activity through the uninhibited Gq pathway. Thus, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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